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Pathophysiology in postterm pregnancy - Epidemiology, risk factors and cervical ripening

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ABSTRACT

Background: Postterm pregnancy, defined as a pregnancy of 42 or more completed weeks of gestation, occurs in approximately 5-10 % of all pregnancies. The condition is associated with increased maternal and fetal morbidity as well as an increased risk of perinatal mortality. The risk of postterm pregnancy is higher among women who are nulliparous and of advanced maternal age. Genetic predispositions may also contribute to an increased risk of postterm pregnancy. Certain characteristics, notably obesity, advanced maternal age and nulliparity are common in women with delayed parturition and are also common among women with polycystic ovary syndrome (PCOS). However, outcomes of pregnancy among women with PCOS have been difficult to investigate due to confounding variables. Normal and delayed parturition is a complex and poorly understood process. A key component of normal parturition is the inflammatory process in the cervix, termed "cervical ripening", which precedes normal labor. The physiology of cervical ripening, the causes of absent cervical ripening postterm, and why some women do not respond with adequate cervical ripening after administration of prostaglandins, are not properly understood. This thesis aims to describe risk factors for postterm pregnancy and failed labor induction, to investigate expression of prostaglandin receptors and cytokines in postterm women with failed and successful labor induction, as well as investigating the association between polycystic ovary syndrome, postterm pregnancy and adverse pregnancy outcomes.

Methods: In paper I, risk factors for postterm pregnancy were determined using data from the Swedish Medical Birth Registry (MBR) where a cohort of term and postterm singleton births, taking place between 1992 to 2006 (total n=1,176,131), was identified. In paper II, a cohort of singleton births from 1995 to 2008 (n=1,191,336) was identified in the Swedish Medical Birth Registry, out of which 3,787 were born to a mother with a previous diagnosis of PCOS. In paper III and IV, transvaginal cervical biopsies were taken from non-pregnant, term pregnant and postpartal women as well as from postterm women with failed and successful labor induction. The biopsies were analyzed for mRNA expression with real-time PCR (RT-PCR). Immunohistochemistry was performed to analyze expression and distribution of cytokines (IL-1β, IL-6, IL-8, IL-10 and IL-18), prostaglandin receptors (EP1-4 and FP) and stroma factors (CTGF, calgranulin B, furin and ALOX 15).

Results: We identified advanced maternal age, nulliparity and BMI > 30.0 kg/m^2 as risk factors for postterm pregnancy and cesarean section following labor induction postterm. We found that a previous diagnosis of PCOS was not associated with postterm pregnancy. However, we found that independently from assisted reproductive technology and BMI, infants born to women with PCOS were at increased risk of adverse pregnancy outcome. In paper III and IV, we found that impaired cervical ripening in postterm women with failed labor induction was associated with a an elevated value of the ratio in the mRNA expression of EP3 and EP4. We also found an overall down-regulation of pro- and anti-inflammatory cytokines.

Conclusions: The results imply that pregnant women with PCOS should be considered as a high risk group of adverse pregnancy outcomes and the obstetric guidelines should be reviewed. Women with postterm pregnancy are obese, nulliparous and of advanced age as compared to others. Down-regulation of pro- and anti-inflammatory cytokines among women with impaired cervical ripening as well as differences between women in the expression of EP3 and EP4 provides important information for an improved understanding of the physiology of normal and delayed parturition.

Key words: *Postterm pregnancy, cervical ripening, cytokines, prostaglandin receptors, labor induction, polycystic ovary syndrome, obesity, cesarean section*

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